Claim Listing

Amendments to the claims are reflected in the following listing of claims, which replaces all prior versions or listings of the claims.

1 – 55. (Cancelled)

56. (withdrawn) A method of evaluating whether an organic non-peptide compound can promote a wild-type activity in a mutant form of a mammalian protein of the p53 family, wherein one or more functional activities of said protein are at least partially impaired by the inability of said protein to maintain a functional conformation under physiological conditions, said method comprising the steps of:

(a) contacting said mutant protein with an organic non-peptide compound that is capable of binding to one or more domains in said mutant protein under physiological conditions and stabilizing a functional conformation therein; and,

(b1) permitting said stabilized protein to interact with one or more macromolecules that participate in said wild-type activity with measurement of said activity; or

(b2) confirming the presence of said functional conformation via a method selected from the group consisting of chromatography, spectroscopy, absorption, ultracentrifugation, specific DNA binding assays, and protein binding of another gene product known to be inhibited or activated by p53.

57. (New) A method of screening organic non-peptide compounds for stabilizers of proteins of the p53 family comprising:

contacting a mammalian p53 family polypeptide or fragment thereof with an organic, non-peptide compound, and

measuring interaction between the compound and the polypeptide or fragment thereof, and measuring an effect of the compound on restoring or stabilizing a functional conformation of the polypeptide, wherein a compound that binds the polypeptide or fragment and restores or stabilizes a functional conformation is selected as a compound that stabilizes proteins of the p53 family.

58. (New) The method of claim 57, wherein the interaction is binding between the compound and the polypeptide.

59. (New) The method of claim 58, wherein said contacting and measuring are conducted at a temperature of approximately 20 °C to 50 °C.

60. (New) The method of claim 58, wherein binding is measured under physiological conditions.

61. (New) The method of claim 58, wherein effects on functional conformation are measured at physiological conditions.

62. (New) The method of claim 58, wherein binding is measured at a concentration of the compound of 1mM or less.

63. (New) The method of claim 58 that is performed in a cell-free environment.

64. (New) The method of claim 58, wherein the polypeptide is an isolated polypeptide.

65. (New) The method of claim 58, wherein the polypeptide comprises a p53 DNA binding domain, and wherein a monoclonal antibody that is specific for the p53 DNA binding domain is used to anchor the polypeptide to a solid phase surface for use in the contacting and measuring steps.

66. (New) The method of claim 58, wherein the measuring of binding comprises anchoring said polypeptide or said compound onto a solid phase surface and detecting polypeptide-compound complexes.

67. (New) The method of claim 66, wherein the polypeptide is anchored on a solid phase surface and the compound is labeled with a label.

68. (New) The method of claim 67, wherein the label is a radioisotope or a fluorescent label.

69. (New) The method of claim 58, wherein the measuring of restoration or stabilization of functional conformation comprises:

contacting the polypeptide with a conformationally-sensitive antibody whose binding to an epitope of p53 is dependent upon the presence of native p53 conformation, in the presence, and also the absence, of said compound, and measuring the amount of the antibody bound to the polypeptide.

70. (New) The method of claim 69, wherein the antibody or the polypeptide is bound to a solid support, and wherein the measuring comprises measuring the amount of antibody-polypeptide complex bound to the support in the presence and absence of the compound.

71. (New) The method of claim 69, wherein the polypeptide comprises a p53 DNA binding domain, and wherein a monoclonal antibody that is specific for the p53 DNA binding domain is used to anchor the polypeptide to the solid phase surface.

72. (New) The method of claim 58, wherein the contacting and measuring steps are performed simultaneously by detecting a conformational change of said polypeptide or fragment in the presence of said compound.

73. (New) The method of claim 58, wherein the measuring of binding and restoration or stabilization of conformation comprises:

contacting the polypeptide with an antibody that specifically recognizes a conformationally sensitive epitope of p53, and

determining whether the antibody binds to the polypeptide in the presence of the compound.

74. (New) The method of claim 73, wherein the presence of the epitope in p53 polypeptides correlates with at least one wild-type physiological activity of p53.

75. (New) The method of claim 73, wherein the existence of a defect in the epitope in p53 polypeptide correlates with at least one inactivated state of p53.

76. (New) The method of claim 73, wherein said antibody is mAb 1620 or mAb 240.

77. (New) The method of claim 73, wherein the antibody is mAb 240, and wherein the polypeptide is a temperature sensitive mutant form of p53 possessing an epitope recognized by mAb 240.

78. (New) The method of claim 73, wherein the determining of antibody binding comprises contacting with a labeled antibody that recognizes the antibody specific for the epitope of p53, and measuring labeled antibody attached to complexes of the polypeptide and the antibody that recognizes the epitope.

79. (New) The method of claim 58, further comprising tumor screening the compound *in vivo* for ability to halt or repress tumor growth, wherein a compound that binds the polypeptide or fragment and restores or stabilizes a functional conformation, and halts or represses tumor growth *in vivo* is selected as a compound that stabilizes proteins of the p53 family.

80. (New) The method of claim 58, further comprising tumor screening the compound *in vitro* for ability to halt or repress tumor growth, wherein a compound that binds the polypeptide or fragment and restores or stabilizes a functional conformation, and halts or represses tumor growth *in vitro* is selected as a compound that stabilizes proteins of the p53 family.

81. (New) The method of claim 80, wherein the tumor screening is performed using: (a) tumor cells that express a mutant of p53 protein; or (b) a cell line that expresses a mutant of p53 protein.

82. (New) The method of claim 58, wherein the p53 family polypeptide or fragment is human.

83. (New) The method of claim 58, wherein the p53 family polypeptide or fragment is selected from the group consisting of p53, p63, p73, and fragments of p53, p63, and p73.

84. (New) The method of claim 83, wherein said polypeptide comprises the p53, p63, or p73 DNA binding domain.

85. (New) The method of claim 83, wherein said polypeptide comprises a full length p53, p63, or p73 protein.

86. (New) The method of claim 58, wherein the p53 family polypeptide or fragment is human p53 or a fragment thereof.

87. (New) The method of claim 86, wherein said polypeptide comprises the p53 DNA binding domain.

88. (New) The method of claim 87, wherein the p53 DNA binding domain is wild-type.

89. (New) The method of claim 87, wherein said polypeptide comprises the p53 DNA binding domain without the entire N and C terminal domains.

90. (New) The method of claim 58, wherein the polypeptide used to measure the binding is a p53 fragment.

91. (New) The method of claim 90, wherein the polypeptide used to measure the binding is a p53 fragment that comprises the p53 DNA binding domain.

92. (New) The method of claim 91, wherein the DNA binding domain of said polypeptide is destabilized compared to the wild-type.

93. (New) The method of claim 58, wherein said polypeptide is a full-length mutant p53 protein.

94. (New) The method of claim 58, wherein the polypeptide comprises a p53 DNA binding domain containing a missense mutation.

95. (New) The method of claim 58, wherein the polypeptide comprises a p53 DNA binding domain containing one or more mutations that render it susceptible to misfolding.

96. (New) The method of claim 95, wherein the polypeptide comprises a full length p53 protein or fragment thereof, said protein or fragment containing one or more mutations at one or more of residue positions 132, 135, 138, 141, 143, 146, 151, 152, 154, 157, 158, 159, 163, 173, 176, 179, 186, 194, 196, 213, 220, 237, 238, 241, 242, 258, 266, 272, 278, 280, 281, 285, 286, 175, 245, 248, 249, 273, and 282.

97. (New) The method of claim 96, wherein the polypeptide comprises one or more mutations selected from the group consisting of 143A, 173A, 241D, 175S, 249S, and 273H.

98. (New) The method of claim 58, wherein measurement of the effect on polypeptide conformation is performed by at least one method selected from the group consisting of chromatography, spectroscopy, absorption, ultracentrifugation, and specific DNA binding assays.

99. (New) The method of claim 58 further comprising designing an additional compound that promotes a wild-type activity of a protein of the p53 family wherein said compound is used to generate a hypothesis, identifying a candidate compound that fits the hypothesis, and measuring whether the candidate compound promotes a wild-type activity of the p53 family.

100. (New) A method of screening organic non-peptide compounds for stabilizers of proteins of the p53 family comprising:

contacting an organic, non-peptide compound and a polypeptide that comprises a DNA binding domain of a mammalian p53 protein, wherein the polypeptide comprises a conformation-sensitive epitope of p53; and

measuring the conformation of the epitope with a conformation-sensitive antibody, wherein a compound that restores or stabilizes a functional conformation of the polypeptide is selected as a compound that stabilizes proteins of the p53 family.

101. (New) A method of screening organic non-peptide compounds for stabilizers of proteins of the p53 family comprising:

contacting an organic, non-peptide compound and a polypeptide that comprises a DNA binding domain of a mammalian p53, p63, or p73 protein, wherein the polypeptide binds to a DNA; and

measuring binding between the polypeptide and the DNA, wherein a compound that restores or stabilizes binding between the polypeptide and the DNA is selected as a compound that stabilizes proteins of the p53 family.

102. (New) The method of claim 101, wherein the polypeptide lacks a p53 transcriptional activation domain.

103. (New) The method of claim 101, wherein the polypeptide lacks a p53 oligomerization domain.